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Short report

Phase II trial of the oral platinum complex JM216 in non-small-cell lung cancer: An EORTC early clinical studies group investigation

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Summary

Background: JM216 is a new oral platinum complex with dose-limiting toxicity myelosuppresssion, now undergoing phase II evaluation.

Patients and methods: JM216 was evaluated as first line therapy in non-small-cell lung cancer. Seventeen patients received 120 mg/m^2/day for five days repeated every three weeks.

Results: Toxicity was manageable, the commonest side-effects being nausea, vomiting, diarrhoea, constipation and asthenia. Myelososuppression was generally grade < 2 and there were no cases of neutropenic sepsis or bleeding. Thirteen patients were fully evaluable for response. No sustained objective responses were reported. One patient was reported as stable disease had a partial response after three courses but was progressing again after four. An additional five patients had stable disease (46.2%).

Conclusions: Although some patients may have had useful palliation, JM216 did not appear to have significant antitumour activity in non-small-cell lung cancer.

Key words: JM216, lung cancer, non-small cell, oral chemotherapy, platinum

Introduction

Lung cancer is one of the leading causes of death in men and women [1]. Non-small-cell lung cancer usually presents as a systemic disease for which palliative treatment only is available. Single agent chemotherapy has been studied extensively in this disease, with cisplatin producing the most consistent response rates in the region of 20% [2]. An oral platinum agent with mild toxicity would be of value in this setting.

The ammine/amine platinum (IV) dicarboxylates [3] were developed with the intention that their enhanced lipophilicity and stability would both improve drug absorption and reduce local toxicity within the gut compared with cisplatin and carboplatin. Bis(acetatato) ammine cyclohexylamine dichloro platinum (IV), or JM216, was chosen for clinical development due to superior oral activity *in vivo* compared with cisplatin, carboplatin and tetraplatin [4], and a favourable toxicity profile with dose-limiting myelosuppression [5, 6].

In a phase I study of JM216 using a single oral dose daily × 5 every three to four weeks, the maximum tolerated dose was 140 mg/m^2/day. The dose-limiting toxicity was myelosuppression, non-haematological toxicities were mild and some evidence of antitumour activity was observed [7]. Starting doses of 100 mg/m^2/day × 5 for previously treated patients and 120 mg/m^2/day × 5 for previously untreated patients were recommended for phase II evaluation using this schedule. This phase II study was conducted in previously untreated patients with locally advanced, unresectable or metastatic non-small-cell lung cancer.

Patients and methods

Eligibility

Inclusion criteria were histologically or cytologically verified non-small-cell lung cancer ≥ 1, bidimensionally measurable lesion, WHO performance status (PS) ≤ 2, age ≥ 18 years, adequate bone marrow function, creatinine < 140 μmol/l and if > 100 μmol/l a creatinine clearance ≥ 60 ml/min, bilirubin < 26 μmol/l and transaminases $\leq 2\times$ upper limit of normal unless due to known liver metastases. Exclusions were prior chemotherapy, radiotherapy < 4 weeks previously or to the indicator lesion, and brain or meningeal disease. All patients were required to give informed consent according to local ethical committee guidelines.

Pharmaceutical and treatment information

JM216 was provided by Bristol-Myers Squibb as 10 mg, 50 mg and 200 mg capsules and given at a starting dose of 120 mg/m^2/day × 5 every three weeks or upon bone marrow recovery, i.e. WBC $\geq 3.5 \times 10^9$/l, neutrophils $\geq 1.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l. Treatment could be delayed in the case of renal toxicity grade > 1, neurotoxicity grade > 1 and any other unresolved toxicity apart from alopecia Dose modifications were: dose reduction to 100 mg/m^2/day for grade 4 neutropenia or thrombocytopenia, grade 2 neurotoxicity, or other

grade 3 non-haematological toxicity apart from gastrointestinal or alopecia, withdrawal for grade ≥ 2 nephrotoxicity, grade ≥ 3 neurotoxicity, grade 4 other toxicity; dose increase to 140 mg/m^2/day $\times 5$ in the absence of grade 2 haematological toxicity at nadir or other significant toxicities. Patients were considered evaluable for response after two cycles, progression after one cycle designating early progression. Concurrent radiotherapy for pain outside the indicator lesion(s) was permitted. The choice of antiemetic treatment was not specified and a variety of different regimens were used.

Toxicity and response evaluation

Toxicities were graded according to NCI Common Toxicity Criteria and serious adverse events were reported immediately to the Study Coordinator. Tumour evaluation was performed prior to and after every two cycles of treatment. Physical examination and assessment of performance status were performed every three weeks, plasma biochemistry every three weeks and full blood count weekly. Responses were evaluated according to standard WHO criteria.

Results

Patients and treatment

Eighteen patients were registered, 13 male, 5 female, with a mean age of 61 years (range 45–79), 12 patients were PS 1 and 6 PS 2. Five patients had prior surgery, three prior radiotherapy, and none prior systemic treatment. Nine patients had metastatic disease other than hilar lymphadenopathy at the time of treatment, an additional three patients had disease in mediastinal nodes.

One patient received no treatment, three received incomplete treatment during the cycle two and one received 1/5 the appropriate dose in error. A total of 38 courses were administered, four patients received ≥ 1 dose reductions, in two due to myelosuppression, in one due to grade 3 diarrhoea, and in one due to a prescribing error. In four patients the dose was increased to 140 mg/m^2/day. Treatment delay occurred in 11 patients with delays from 1–14 days (median seven days) in six patients due to myelosuppression, in five unrelated to treatment. Twelve patients had ≥ 2 courses, two patients received five courses.

Toxicity

Principal non-haematological toxicities were nausea and vomiting, diarrhoea, constipation and asthenia. Gastrointestinal toxicity is given in Table 1. Only 10 patients (55%) received a $5HT_3$ antagonist with their first course of JM216, two additional patients received one subsequently. The remaining patients received dopamine antagonists and steroids only. Three patients reported grade 3 asthenia which was possibly drug related. One patient had grade 3 focal motor neurological toxicity, probably related to occult disease progression. All other non-haematological toxicities were grade ≤ 2.

Table 1. Incidence of gastrointestinal toxicity in 17 patients receiving JM216 as defined by worst CTC grade per patient.

	Maximum CTC grade per patient				
	0	1	2	3	4
Nausea	5	5	5	2	–
Vomiting	5	4	6	1	1
Diarrhoea	12	1	3	1	–
Constipation	9	5	2	1	–

Haematological toxicity was easily manageable. Anaemia was usually grade ≤ 1 and never > 2. Most courses (28 of 38) were associated with grade ≤ 1 thrombocytopenia but there were three cases of grade 3 thrombocytopenia and three of grade 4. The median platelet nadir fell from 123×10^9/l after course 1 to 54×10^9/l after course 5, but few patients received > 2 courses making it difficult to draw conclusions from this observation. The majority of patients had no significant leukopenia which was grade ≤ 1 in 32 of 38 courses. Only one patient had grade 3 leukopenia and two grade 3 neutropenia. There were no cases of serious drug-related sepsis.

Most serious adverse events were due to disease progression. Treatment was stopped due to toxicity in three patients, in each case because of myelosuppression, in two cases prolonged leukopenia and thrombocytopenia, in one case grade 4 thrombocytopenia.

Response

Only 13 patients were fully evaluable for response. Reasons for exclusion were early death in one patient, treatment discontinuation in one following myocardial infarction after two cycles, follow-up evaluation either not done or performed at the wrong time in two and failure to receive treatment in one. There were no sustained objective responses to JM216. One patient had a partial response in the primary tumour after three cycles, as measured by CT scan, but was progressing again after four cycles. The tumour remained smaller than at the start of treatment and the patient was recorded as stable disease. An additional five patients were reported as no change. Four patients continued treatment after two cycles due to stable disease or symptomatic benefit. There were seven cases of progressive disease, four of them early.

Discussion

The oral platinum complex JM216 was well tolerated in this group of patients with non-small-cell lung cancer. Subjective toxicities were generally $\leq$ grade 2 although nausea, vomiting, diarrhoea and asthenia could be more severe. Haematological toxicity was surprisingly low with almost no grade > 2 leukopenia or neutropenia. Neutropenic sepsis was not observed. Thrombocytopenia was more frequent but was grade ≤ 2 following 84% of courses administered. There were no problems with bleeding related to thrombocytopenia. Four patients (23% of patients treated) had their dose increased from

120 to 140 mg/m^2/day. Treatment delay occurred in six patients due to delayed haematological recovery and therefore it may be more appropriate for treatment to be repeated every four weeks rather than every three as intended in this study.

The lack of objective antitumour activity was disappointing with no sustained objective responses with 13 patients evaluable for response. Nevertheless, of these patients six had stable disease (46.2%) and there was some evidence of disease palliation. In studies with single agent cisplatin, response rates were in the order of 20% [2] and there was also said to be a dose-response relationship. Carboplatin may be somewhat less active, with an overall response rate in the region of 12% [8]. It must be acknowledged that JM216 as a single agent given according to this dose and schedule is inactive in non-small-cell lung cancer but randomised studies would be required to define properly its role in combination with agents of proven activity.

References

1. Cancer Statistics, 1992. CA 1992; 42: 19–38.
2. Kris M, Cohen E, Gralla R. An analysis of 134 phase II trials in non-small cell lung cancer IV. Toronto: World Conference on Lung Cancer 1985; 39.
3. Giandomenico CM, Abrams MJ, Murrer BA et al. Synthesis and reactions of a new class of orally active Pt(IV) antitumour complexes. In Howell SB (ed): Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy. New York. Plenum Press 1991; 93–100.
4. Kelland LR, Abel G, McKeage MJ. Preclinical antitumour evaluation of bis-acetato-ammine-dichloro-cyclohexylamine platinum (IV): An orally active platinum drug. Cancer Res 1993; 53. 2581–6.
5. McKeage MJ, Morgan SE, Boxall FE et al. Preclinical toxicology and tissue distribution of novel oral antitumour platinum complexes: Ammine/amine platinum (IV) dicarboxylates. Cancer Chemother Pharmacol 1994; 33. 497–503.
6. McKeage MJ, Morgan SE, Boxall FE et al. Lack of nephrotoxicity of oral ammine/amine platinum (IV) dicarboxylate complexes in rodents. Br J Cancer 1993; 67: 996–1000.
7. Judson I, McKeage M, Raynaud F et al. A phase I trial of the oral platinum anticancer drug JM216 complex [Af-*bis*(acetato)-B-ammine-cd-dichloro-E-cyclohexylamin platinum (IV)] Ann Oncol 1994; 5 (Suppl 5): 126
8. Bunn PA Jr. Review of therapeutic trials of carboplatin in lung cancer. Semin Oncol 1989; 16 (Suppl 5): 27–33.

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